

**Table 1. Changes in the Utilization of Nitroprusside and Isoproterenol, as Compared with Nitroglycerin and Dobutamine, in 47 U.S. Hospitals from 2012 to 2015.\***

Variable	2012	2013	2014	2015	P Value
No. of inpatients					
Total	1,435,440	1,452,723	1,437,824	1,470,007	—
Per hospital	30,541±12,542	30,909±12,702	30,592±12,685	31,277±12,797	0.06
No. of patients receiving nitroprusside					
Total	17,242	16,761	13,304	8,159	—
Per 1000 inpatients per hospital	9.30±13.41	9.11±12.19	7.71±9.49	4.99±5.13	<0.001
No. of patients receiving nitroglycerin					
Total	21,778	26,465	40,140	47,377	—
Per 1000 inpatients per hospital	16.17±16.53	18.99±14.29	27.70±15.87	30.55±25.76	<0.001
No. of patients receiving isoproterenol					
Total	4,079	4,058	3,335	2,650	—
Per 1000 inpatients per hospital	2.76±2.31	2.66±2.48	2.17±1.90	1.65±1.29	<0.001
No. of patients receiving dobutamine					
Total	11,762	11,848	12,180	12,552	—
Per 1000 inpatients per hospital	8.02±5.14	7.96±5.36	8.24±5.77	8.31±5.65	0.74

\* Plus–minus values are means ±SD.

fute the claim that price increases do not reduce patients' access to these medications. Decreasing demand also indicates a correcting market response to increased prices that may be a valuable restraining force to pharmaceutical price increases.

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Supported by unrestricted philanthropic funding to the Heart and Vascular Institute Center for Healthcare Delivery Innovation, Cleveland Clinic. The funding source had no role in the design or conduct of the study; collection, management, analyses, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Disclosure forms provided by the authors are available with the full text of this letter at [NEJM.org](http://NEJM.org).

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DOI: 10.1056/NEJMc1700244

## Novel Treatments for Airway Disease

**TO THE EDITOR:** The study by Cahill et al. (May 18 issue)<sup>1</sup> shows reductions in airway hyperresponsiveness, mast-cell counts, and tryptase release after treatment with imatinib, a KIT inhibitor, in 62 patients with severe refractory asthma. Targeting mast cells with KIT inhibitors is indeed an appealing, innovative approach for severe asthma. We have previously investigated another KIT inhibitor, masitinib, in 44 patients with

severe glucocorticoid-dependent asthma.<sup>2</sup> At 16 weeks of treatment, a similar reduction in oral glucocorticoids was observed with masitinib and placebo. However, the Asthma Control Questionnaire score showed significantly better control in the masitinib group than in the placebo group. Furthermore, a bronchial epithelial KIT-positive subpopulation exists and is increased in asthma.<sup>3</sup> We thus propose that KIT inhibitors may target

various cell types besides mast cells in asthma, including bronchial epithelial cells.

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Dr. Humbert reports receiving lecture fees from and serving on advisory boards for AstraZeneca and Teva Pharmaceuticals, receiving lecture and consulting fees from and serving on advisory boards for GlaxoSmithKline and Novartis, and receiving consulting fees from and serving on an advisory board for Roche. Dr. Chanez reports receiving consulting fees from Boehringer Ingelheim, Johnson & Johnson, GlaxoSmithKline, Merck Sharp & Dohme, AstraZeneca, Novartis, Teva Pharmaceuticals, Chiesi, Sanofi, and SNCF, lecture fees from Boehringer Ingelheim, Centocor, GlaxoSmithKline, AstraZeneca, Novartis, Teva Pharmaceuticals, Chiesi, Boston Scientific, and ALK, and industry-sponsored grants from Roche, Boston Scientific, Boehringer Ingelheim, Centocor, GlaxoSmithKline, AstraZeneca, ALK, Novartis, Teva Pharmaceuticals, and Chiesi and serving on advisory boards for Almirall, Boehringer Ingelheim, Johnson & Johnson, GlaxoSmithKline, AstraZeneca, Novartis, Teva Pharmaceuticals, Chiesi, and Sanofi. No other potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1708004

**TO THE EDITOR:** Imatinib mesylate is used as a treatment for chronic myeloid leukemia and gastrointestinal stromal tumors.<sup>1</sup> A better clinical benefit and improved responses in these tumors<sup>2,3</sup> are associated with therapeutic plasma levels of imatinib. The article by Cahill and colleagues examining the effect of imatinib treatment on airway responsiveness in patients with severe refractory asthma has shown proof of the principle that imatinib may have therapeutic benefit in asthma. Because imatinib clearance may be increased after chronic exposure over a period of 12 months,<sup>4</sup> we wondered whether Cahill et al. have samples to assess plasma levels of imatinib to determine whether there is a relationship between such levels and therapeutic effects.

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DOI: 10.1056/NEJMc1708004

**TO THE EDITOR:** Wechsler et al. (May 18 issue)<sup>1</sup> report on the use of mepolizumab in eosinophilic granulomatosis with polyangiitis.<sup>1</sup> In the same issue, Cahill et al. report on the use of imatinib in refractory asthma. Imatinib is already well accepted as a treatment for *FIP1L1-PDGFR*A fusion-associated myeloproliferative hypereosinophilic syndrome, but there are only two reports of its use in eosinophilic granulomatosis with polyangiitis.<sup>2,3</sup> Since April 2016, I have been treating a patient with severe, biopsy-proven, *FIP1L1-PDGFR*A-negative, *JAK2*-negative eosinophilic granulomatosis with polyangiitis. After a lack of response to cyclophosphamide, intravenous immune globulin, rituximab, and reslizumab, the patient's disease remained active during high-dose glucocorticoid treatment. I then began imatinib. Within days, the patient's C-reactive protein level had almost normalized, and he has since been weaned down to 2 mg of prednisone a day.

This is just a single case, and yet for our thinking on the pathogenesis and management of eosinophilic granulomatosis with polyangiitis, it may be important. Our clear success, coupled with the failure of multiple known medications for the disorder, suggests that further research into the roles of the various imatinib-sensitive tyrosine kinases in eosinophilic granulomatosis with polyangiitis is in order.

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1708004

**TO THE EDITOR:** Wechsler et al. report that approximately half the patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis had protocol-defined remission after mepolizumab therapy. The benefit of treatment was slightly greater with respect to asthma relapses and sinonasal relapses than with respect to vasculitis relapses. We wonder whether there was a relationship among the blood eosinophil count, the number of asthma exacerbations in the previous year, and the response to mepolizumab, as is the case for severe eosinophilic asthma.<sup>1</sup> It is conceivable that mepolizumab may be particularly useful for patients who, according to the recently suggested revised nomenclature for eosinophilic granulomatosis with polyangiitis,<sup>2</sup> fulfill the criteria for hypereosinophilic asthma with systemic (nonvasculitic) manifestations.

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DOI: 10.1056/NEJMc1708004

**DR. CAHILL AND COLLEAGUES REPLY:** In our study, we found that treatment with imatinib reduced serum levels of mast-cell tryptase, decreased airway hyperresponsiveness, and improved airway function. Several of these improvements correlated with indexes of reduced mast-cell burden or function. As stated in our article, we recognize that KIT is expressed on cells other than mast cells. Thus, we agree with Martinez-Anton and colleagues that it is possible that the effects we observed could reflect additional effects of imatinib that are unrelated to mast cells. Nonetheless, the observation that changes in airway function correlated with changes in airway tryptase-positive cells suggests that the salutary effect was related to the effect on mast cells.

Regarding the query by Hammoudi and colleagues about whether plasma levels of imatinib might affect efficacy: we did not undertake such measurement. We did assess for an association between participant body weight, which has been suggested to influence plasma levels of imatinib,<sup>1</sup> and our primary clinical outcome, change in airway hyperresponsiveness, and did not observe an association.

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1708004

**DR. WECHSLER AND COLLEAGUES REPLY:** We performed post hoc modeling to explore the relationship between various baseline characteristics and treatment effect. The modeling work provided some evidence of an association between higher baseline blood eosinophil counts and benefits of mepolizumab; however, caution is required in concluding a direct causal relationship because of the strong association between low baseline blood eosinophil counts and a high oral glucocorticoid dose at baseline. A high oral glucocorticoid dose at baseline was a confounding variable for several clinical end points owing to the need to slowly taper oral glucocorticoids and the

increased difficulty of achieving a greater percent reduction in the average daily dose when starting with a higher dose at baseline. No interaction was seen between the number of relapses during the previous 2 years and treatment effect. Overall, the results of the modeling were inconsistent among end points in terms of the strength of the evidence, and caution is needed in concluding any causal relationship between the factors that were evaluated and treatment effect.

Although approved only for eosinophilic asthma,<sup>1,2</sup> mepolizumab has now shown efficacy in eosinophilic granulomatosis with polyangiitis and idiopathic hypereosinophilic syndrome.<sup>3</sup> With its interleukin-5–blocking mechanism of action, it is likely that this therapy will have beneficial effects in other hypereosinophilic conditions, especially in intermediate phenotypes including the recently proposed entity of hypereosinophilic asthma with nonvasculitic systemic manifestations.

As with the patients in our study who did not have a response to mepolizumab, Kedar's case report of a patient who had a response to imatinib therapy after not having a response to other therapies, including reslizumab, highlights the need to do further studies to better understand the underlying pathobiologic mechanisms of eosinophilic granulomatosis with polyangiitis. Although the eosinophil appears to be the

dominant cell implicated in most patients with eosinophilic granulomatosis with polyangiitis, it appears that this is a complex syndrome with several putative causative elements that make it difficult to differentiate from other hypereosinophilic syndromes. Given the apparent benefit of imatinib in Kedar's patient, we agree that future research exploring the role of tyrosine kinase inhibition in eosinophilic granulomatosis with polyangiitis is warranted.

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1708004

## Exercise Type in Dieting Obese Older Adults

**TO THE EDITOR:** In a well-performed clinical trial, Villareal et al. (May 18 issue)<sup>1</sup> found that weight loss plus physical activity improved functional status in obese older adults. Nevertheless, conclusions should be drawn with caution, because there was no weight-loss control group. We cannot differentiate whether the improvement in functional status was caused by weight loss, physical activity, or both. We are asked to assume that the observed increases in physical performance, peak oxygen consumption, and strength are attributable to increased physical activity, whereas the observed decreases in body weight, lean mass, and bone mineral density at the hip are attributable to the reduced-calorie diet. If these assumptions are correct, we would then have to conclude that it could be harmful to recommend weight loss by means of calorie restriction. In-

deed, the “obesity paradox,”<sup>2</sup> observations of lower mortality among obese older adults than among older adults of normal weight, raises further questions about aiming for weight loss as an intervention of choice. We suggest a follow-up study with two comparison groups: one group consuming a calorie-restricted diet and another consuming a healthy diet (e.g., a Mediterranean diet<sup>3</sup> or the DASH [Dietary Approaches to Stop Hypertension] diet<sup>4</sup>) that does not include calorie restriction.

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